

REMARKS

Applicants have added new claims 56-72 and have amended claim 54 to also depend from the new claims.

New claims 56-67 are dependent claims. New claims 56 recites that the Fab fragments are obtained from hyperimmune serum, and new claim 57 recites that the Fab fragments are obtained from animal serum. The application supports these claims at page 6, lines 8-12 ("For example, in the context of antivenin purification, the antibody source may be . . . commercially available antivenins.") and page 4, lines 19-22 ("Antivenin is a suspension of venom-neutralizing antibodies prepared from the serum of animals (typically horses) hyperimmunized against a specific venom or venoms.").

New claim 58 recites that the animal serum has been partially purified by ammonium sulfate precipitation. The application supports this claim at original claim 4 ("partially purified by precipitation procedures"), page 2, lines 8-14 (ACP "is normally purified by ammonium sulfate procedures."), page 6, lines 8-12 ("the antibody source may be . . . commercially available antivenins"), and pages 15-16 ("Derivation of F(ab) Fragments from ACP").

New claim 59 recites that the antivenom pharmaceutical composition further comprises Fab₂ fragments. The application supports this claim at page 3, lines 4-5 ("Furthermore, F(ab) and F(ab)₂ fragments may sometimes be utilized together."), original claim 28 ("An antivenin composition comprising an administrable form of F(ab)₂ fragments"), and page 17, lines 26-27 ("Again, another clear precipitate band against F(ab)₂ is shown. A weak F(ab) reaction is noted along with a slight hint of a F(c) reaction. This would seem to indicate that a 100% digestion to F(ab) fragments was not accomplished in the 4 hour digestion period")]

New claims 60-62 recite that the Fab fragments are obtained from polyvalent, monovalent, and monoclonal antibodies, respectively. The application supports these claims at, for example, page 5, lines 32-34 ("Furthermore, these antibody fragments can be products from monovalent, polyvalent and monoclonal sources.").

New claim 63 recites that the Fab fragments are obtained by digesting a population of antibodies with papain. The application supports these claims at, for example, original claim 1 (“contacting the antibody containing source with a papain-polyacrylamide matrix”) and page 2, lines 36-38 (“exposure of IgG molecules to papain produces F(ab) fragments”).

New claim 64 recites that the population of antibodies is raised to a single venom, and new claim 65 recites that the population of antibodies is raised to more than one venom. The application supports this claim at page 6, lines 8-12 (“the antibody source may be . . . commercially available antivenins”) and page 4, lines 19-22 (“Antivenin is a suspension of venom-neutralizing antibodies prepared from the serum of animals (typically horses) hyperimmunized against a specific venom or venoms.”).

New claim 66 recites that the more than one venom is selected from the group consisting of venom of a snake of the *Crotalus* genus and/or venom of a snake of the *Bothrops* genus, new claim 67 recites that the snake of the *Crotalus* genus is selected from the group consisting of *Crotalus adamanteus*, *Crotalus atrox*, and/or *Crotalus durissus*, and *Bothrops atrox*, and new claim 68 recites that the snake of the *Bothrops* genus is *Bothrops atrox*. The application supports this claim at page 6, lines 8-12 (“For example, in the context of antivenin purification, the antibody source may be . . . commercially available antivenins.”) and pages 15-16 (“Derivation of F(ab) Fragments from ACP”). As shown by that attached Physician’s Desk Reference entry, ACP is raised by hyperimmunizing with venoms from *Crotalus adamanteus*, *Crotalus atrox*, *Crotalus durissus*, and *Bothrops atrox*. [Physician’s Desk Reference (1981) at p. 1920, col. 3.]

New claim 69 recites that the antivenom pharmaceutical composition is in lyophilized form. The application supports this claim at page 6, lines 8-12 (“For example, in the context of antivenin purification, the antibody source may be . . . commercially available antivenins.”) and pages 15-16 (“Derivation of F(ab) Fragments from ACP”). As shown by that attached Physician’s Desk Reference entry, ACP is in lyophilized form. [Physician’s Desk Reference (1981) at p. 1920, col. 3, p. 1922, col. 3.] and page 4, lines 19-22 (“Antivenin is a suspension of venom-neutralizing antibodies prepared from the serum of animals (typically horses) hyperimmunized against a specific venom or venoms.”).

New claim 70 recites that the snakebite victim is a human. The application supports this new claim on page 23, lines 1-3 ("The above data indicates that the F(ab) fragments as well as IgG prepared by the processes of this invention can be used in the treatment of human snake bite victims.").

New claim 71 is an independent claim. Each of its limitations already appears in an existing or new claim, whose support is discussed above.

New claim 72 is an independent claim that is identical to new claim 71 except that new claim 72 recites the Crotalidae family rather than its contained *Crotalus* genus. The application supports this claim at page 2, line 10, which indicates that ACP is indicated for the Crotalidae family, not just the *Crotalus* genus: "Antivenin (**Crotalidae**) Polyvalent" (emphasis added). As shown by that attached Physician's Desk Reference entry, ACP contains antibodies "capable of neutralizing the toxic effects of crotalids" including snakes of the genera *Crotalus*, *Sistrurus*, *Agkistrodon*, *Bothrops*, and *Lachesis*. [Physician's Desk Reference (1981) at p. 1920, col. 3.] As shown by the attached pages from *Snake Venom Poisoning*, these genera all belong to the Crotalidae family. [Russell, F.E., "Identification and Distribution of North American Venomous Snakes," Ch. 3 in *Snake Venom Poisoning* (1983) at p. 51] The application tested the lethality neutralizing properties of the Fab fragments of the invention and concluded that the Fab fragments derived from ACP "retain their activities" and even "have specific activities much greater than that of Wyeth antivenin," because "the therapeutically active portion of [the antibody] remains." [Page 23, lines 5-7, 15-21.] Accordingly, one skilled in the art would recognize that the antivenom composition of the invention would neutralize the lethality of the venom of a snake of the Crotalidae family, just as ACP does before having its Fab fragments isolated.¹

Upon entry of this amendment, claims 40-52, 50, and 54-72 will be pending in this application, with claims 54-55 being withdrawn from reconsideration.

I. Request for Rejoinder Upon Indication of Allowable Claims

¹ Applicants address their arguments below to the claims previously addressed by the PTO, which recited the *Crotalus* genus, but the arguments apply equally to the new claims, including the recitation of the Crotalidae family.

Claims 54-55 are method claims that multiply depend from product claims 40-42 and 50, and 54-72. Upon an indication of allowable claims for the elected subject matter, Applicants would be entitled to have such method claims considered after an indication of allowability of the product claims from which they depend. MPEP § 821.04(b) ("if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder.") As suggested by the MPEP to expedite prosecution, Applicants have already presented these claims rather than present them after an indication of allowability of the product claims. MPEP § 821.04(b) ("In view of the rejoinder procedure, and in order to expedite prosecution, applicants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution.").

"Process claims which depend from or otherwise require all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier." MPEP § 821.04(b)(emphasis added). Accordingly, if the product claims are found allowable, process claims 54-55 must be rejoined and examined in this application.

II. Procedural History

In view of the complicated procedural history of this application, Applicants will briefly summarize that history. This application was filed on March 15, 1995 claiming priority from a series of applications, including original parent application Serial No. 06/659,629, filed October 9, 1984. During prosecution, Applicants submitted extensive evidence of the nonobviousness of the claimed invention, including:

- Declaration of Damon Smith, Ph.D. dated April 24, 1995²
- Declaration of John Sullivan, M.D. dated September 25, 1995
- Declaration of Findlay Russell, M.D., Ph.D. dated April 30, 1998³

² An earlier Declaration of Damon Smith, Ph.D. dated December 20, 1994 was filed, but it contained a typographical error that was corrected in the Declaration dated April 24, 1995.

The Examiner maintained the rejections, and applicants filed an Appeal Brief to the Board on February 12, 1999. The rejections on appeal were

1. Written description rejection of claims 40-42 and 45-47 under § 112
2. Obviousness rejection of claims 40-42 and 45-47 under § 103 over the Sullivan article⁴ in view of the Coulter article⁵ and the Smith article⁶, as evidenced by Stedman's Medical Dictionary.
3. Obviousness rejection of claims 45-47 under § 103 over the Sullivan article in view of the Coulter article

The Board mailed a Decision on Appeal on January 29, 2003, reversing the written description rejection, vacating the first obviousness rejection (claims 40-42 and 45-47) and affirming the second obviousness rejection (claims 45-47). [First Decision on Appeal at p. 2.] The Board also introduced a new ground for rejection under 37 C.F.R. § 1.196(b), rejecting claims 40-42 over the Sullivan Article in view of the Coulter article. [First Decision on Appeal at pp. 9-10.] The Board based its rejection on its belief that it would have been obvious to produce Fab fragments against *Crotalus* for use in assays, and that the recitation by claims 40-42 of an "antivenom" was merely a new use for an otherwise old or obvious composition, which cannot render a claim patentable under *In re Zierden*, 411 F.2d 1325 (CCPA 1969), and *In re Pearson*, 494 F.2d 1399 (CCPA 1974). [First Decision on Appeal at pp. 7, 9-10.]

Applicants responded to the new ground for rejection by amending the claims to further specify that the antivenom composition was a pharmaceutical composition for treating a snakebite victim and that the anivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus, as shown below:

³ This is entitled the "First Declaration of Findlay E. Russell, M.D., Ph.D." The Second Declaration of Findlay E. Russell, M.D., Ph.D is irrelevant to the obviousness rejection, and Applicants will only discuss the first Russell Declaration in this Amendment.

⁴ Sullivan et al., 25 Proc. West. Pharmacol. Soc. 185-192 (1982).

⁵ Coulter et al., 59 J. Immunol. Mtds. 199-203 (1983).

⁶ Smith et al., 36 Clin. Exp. Immunol. 384-396 (1979).

40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus

[Amendment filed March 31, 2003 at pp. 1-2.] The Examiner maintained the obviousness rejections, and Applicants filed a second Appeal Brief on July 6, 2004.

The Board mailed a Decision on Appeal on March 30, 2006, affirming the rejection of claims 40-42 and 50 under § 103 over the Sullivan article in view of the Coulter article and not reaching the rejection of claims 40-42 and 50 under § 103 over the Sullivan article in view of the Coulter article, the Smith article, and Stedman's Medical Dictionary. [Second Decision on Appeal at p. 2.] As in the first Appeal, the Board again based its decision on its belief that Applicants were merely stating a new use for an otherwise old or obvious composition, which cannot render a claim patentable under *In re Zierden* and *In re Pearson*. [Second Decision on Appeal at p. 8-13.] Moreover, the Board refused to consider the Smith, Sullivan, and Russell Declarations because they related to the use of the claimed composition as an antivenom. [Second Decision on Appeal at p. 13 n. 7.]

Applicants appealed under § 142 to the Court of Appeals for the Federal Circuit, filing a Brief of Appellants on October 11, 2006. The Federal Circuit vacated the Board's decision "because the Board failed to give any weight to the rebuttal evidence of record." *In re Sullivan*, 498 F.3d 1345, 1347 (Fed. Cir. 2007) (attached). Moreover, the Federal Circuit found that "the Board's focus on the intended use of the claimed composition misses the mark." Unlike the applicant in *Zierden*, Applicants did not concede that the intended use was the only factor distinguishing the prior art. Rather, Applicants extensively argued that the claimed invention "exhibited the unexpected property of neutralizing the lethality of rattlesnake venom while reducing the occurrence of adverse immune reactions in humans. Such a use and unexpected property cannot be ignored." *Id.* at 1353.

According to the Federal Circuit, the issue was “not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use.” *Id.* Accordingly, that unexpected use was relevant, as well as the Declarations describing it, should have been considered. *Id.*

On remand from the Federal Circuit, the Board again affirmed the rejections of claims 40-42 and 50 under § 103 over the Sullivan article in view of the Coulter article and not reaching the rejection of claims 40-42 and 50 under § 103 over the Sullivan article in view of the Coulter article, the Smith article, and Stedman’s Medical Dictionary. [Third Decision on Appeal at p. 4.] The Board first asserted that “there is no requirement in claim 40 that its composition be used pharmaceutically, as opposed to its use in performing *in vitro* assays” [Third Decision on Appeal at p. 17] and that “it cannot be overstated that the claimed invention is drawn to a composition, not a method of treatment.” [Third Decision on Appeal at p. 21.] The Board also found that one of ordinary skill in the art would have a reasonable expectation that Fab fragments would neutralize the lethality of a venom of a snake of the *Crotalus* genus because the Coulter article teaches that its Fab fragments “retain their ability to neutralize the toxicity of a snake venom toxin.” [Third Decision on Appeal at pp. 18, 19 (“Coulter teaches that Fab fragments retain their intact parent immunoglobulin’s ability to neutralize the lethality of snake venom toxin.”), 20 (“Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake venom.”), 20-21 (“Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom.”), 21 (“Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake venom.”), (“Coulter supplied the key element required to satisfy the long-felt need”), p. 23 (“Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom”).]

Applicants filed a civil action to obtain a patent under § 145 in the United States District Court for the District of Columbia on August 14, 2009. In the complaint, Applicants alleged:

24. Additional evidence not of record in the PTO further confirms that claims 40-42 and 50 of the ‘454 application comply with 35 U.S.C. § 103(a) and should therefore be allowed. For example, and without limitation, soon after CroFab® (i.e., a product embodying the invention) was first marketed in the United

States, the only other commercially-available rattlesnake antivenom was withdrawn from the market because it caused many side effects and was less safe than CroFab®. The life-saving properties of CroFab® have been featured on a multi-part program for the television series “Animal ER.” CroFab® is projected to have sales in the U.S. of over US\$30 million in 2009.

In response to these allegations, the USPTO determined “that remand to the agency is warranted.” [Unopposed Motion for Remand at p. 2 (attached).] Remand would “allow the agency to consider Protherics’ evidence in the first instance and to evaluate whether that new evidence establishes the patentability of Protherics’ claimed invention.” [Unopposed Motion for Remand at p. 2.] The District Court Judge granted the Unopposed Motion. [Order dated May 11, 2001 (attached).] The Board subsequently remanded this application “to the Examiner for further proceedings consistent with the order of the District Court” “for further consideration of new evidence.” [Order Remanding to Examiner at p. 1.]

Applicants accordingly submit this Amendment and its supporting evidence. Applicants will discuss this evidence in the context of the pending rejections. Specifically, Applications will address the pending rejections as set forth by the Board in the Third Decision on Appeal, which is the last substantive paper from the PTO.

III. The USPTO has not established a prima facie case of obviousness

Claims 40-42 and 50 stand rejected under § 103 as being obvious over the Sullivan article in view of the Coulter article, and claims 40-42 and 50 also stand rejected under § 103 as being obvious over the Sullivan article in view of the Coulter article, the Smith article, and Stedman’s Medical Dictionary. Applicants traverse on the grounds that the PTO has not made a prima facie case and, even if the PTO had done so, Applicants’ rebuttal evidence establishes that claims 40-42 and 50 (as well as the new claims) are patentable.

A. The Federal Circuit did NOT find a prima facie case had been established

Initially, Applicants respectfully note that the Third Decision on Appeal mischaracterizes the Federal Circuit’s findings. The Third Decision is premised upon the mistaken belief that “the

Federal Circuit held that a prima facie case of obviousness has been established on this record.” [Third Decision on Appeal at p. 5.] But the Federal Circuit very clearly did not hold that a prima facie case had been established. This is perhaps best illustrated by a partial sentence from the Federal Circuit’s opinion as quoted by the Third Decision with that entire sentence from the Federal Circuit’s opinion. The Third Decision asserts:

The Federal Circuit found that a “prima facie case of obviousness was established [in this case] because Sullivan teaches whole antibodies for use against rattlesnake venom and Coulter teaches using Fab fragments to detect venom of a different snake.”

[Third Decision on Appeal at p. 2.] However, considering the entire sentence quoted by the Third Decision reveals that this sentence merely accepted that a prima facie case had been established for purposes of deciding the appeal. Highlighting the text omitted from the quoted sentence by the Third Decision, that sentence reads:

We accept, however, that a prima facie case of obviousness was established because Sullivan teaches whole antibodies for use against rattlesnake venom and Coulter teaches using Fab fragments to detect venom of a different snake.

Sullivan, 498 F.3d at 1351 (emphasis added to show omitted text); see also *id.* at 1352 (“**Accepting that there was a prima facie obviousness case**, however, there was rebuttal evidence.”)(emphasis added).

Indeed, the Federal Circuit started the paragraph containing this sentence by making very clear that it was merely assuming—not deciding—that a prima facie case had been established for purposes of deciding the issues presented in the appeal. “**For purposes of this appeal, we assume** that the Board established a prima facie case of unpatentability under § 103.” *Sullivan*, 498 F.3d at 1351 (emphasis added). Accordingly, the Third Decision is incorrect; the Federal Circuit did not hold that a prima facie case had been established.

B. The USPTO has NOT established a prima facie case

The USPTO published Guidelines in 2007 “to assist Office personnel to make a proper determination of obviousness under 35 U.S.C. § 103, and to provide an appropriate supporting

rationale in view of the recent decision by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 55 U.S. 398 (2007)." Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57526 col. 1 (October 10, 2007). These Guidelines are incorporated in the MPEP at §§ 2141 and 2143.

The Third Decision provides three rationales to support the obviousness rejections: 1) Applicants merely combined prior art elements according to known methods to yield predictable results [Third Decision at p. 13 (quoting *KSR*)], 2) Applicants merely used a known technique to improve similar devices in the same way [Third Decision at pp. 13, 16 (both quoting *KSR*)], and 3) that there was a teaching in the prior art that would have led one of ordinary skill in the art to combine the teachings of the Sullivan article and the Coulter article [Third Decision at pp. 19, 20, 21]. Each of these rationales requires factual support that does not exist in the present case, and the absence of that factual support precludes a rejection on each of these grounds.

The MPEP and Guidelines require that, to establish a *prima facie* case under the first rationale:

Office personnel **must** articulate the following:

- (1) a finding that **the prior art included each element claimed**, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
- (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods . . . ;
- (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination **were predictable**; and
- (4) whatever additional findings

MPEP § 2143 A. Combining Prior Art Elements According to Known Methods To Yield Predictable Results, at p. 2100-129, col. 1 (emphasis added); 72 Fed. Reg. at 57529, cols. 1-2. Not only must each of these findings be articulated, but this rationale cannot be used if a single one of these findings cannot be made. MPEP § 2143 A. at p. 2100-129, col. 1 ("If any of these findings

cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.”); 72 Fed. Reg. at 57529, col. 2 (same).

This rationale cannot support the obviousness rejections because the prior art did not teach each element claimed, and the invention yielded unpredictable results. The Third Decision relies upon the Coulter article as teaching Fab fragments neutralize the lethality of a venom of a snake, but the Coulter article does not teach that. Rather, the Coulter article teaches that Fab fragments neutralize the lethality of **a single toxin** of a venom. [Dart Declaration at ¶¶ 18-19; Russell Declaration at ¶ 47.]

Snake venoms are a complex mixture of many different components and many different toxins. [Dart Declaration at ¶ 22; Russell Declaration at ¶¶ 15, 47.] The full composition of snake venoms was unknown in 1984, as was the pharmacological effect of some of their constituent toxins. [Dart Declaration at ¶ 22; Russell Declaration at ¶¶ 15-16, 47.] The textilotoxin that Coulter used is a single toxin of the venom of *Psuedonaja textilis*, which was known in 1984 to contain several other medically important toxins. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 47.] Coulter et al. showed that Fabs raised to a single toxin “isolated from the venom of the Australian brown snake, *Psuedonaja textilis*” [Coulter article at p. 199, last sentence] neutralized the lethality of **that single toxin**. [Coulter article at p. 201 third full paragraph.] [Dart Declaration at ¶ 18; Russell Declaration at ¶ 47.] Coulter et al. raised Fab fragments to textilotoxin (not whole venom) and tested those Fab fragments “for their ability to neutralize the lethal effects of textilotoxin [not whole venom] in mice.” [Coulter article at p. 201 third full paragraph; Dart Declaration at ¶¶ 18-19; Russell Declaration at ¶¶ 46-47.]

The Third Decision repeatedly mischaracterizes the teachings of the Coulter article, confusing the distinctions between an individual toxin of a snake venom and the entire snake venom. [Dart Declaration at ¶ 19.] For example, the Decision states:

Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 20, first paragraph (emphasis added).]

Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at sentence bridging pp. 20-21 (emphasis added).]

Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 21, last paragraph (emphasis added).]

Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake **venom**.

[Coulter article at p. 23, second full paragraph (emphasis added); Dart Declaration at ¶ 19.]

None of these statements is true. [Dart Declaration at ¶ 20.] The Third Decision appears to recognize this distinction between a whole venom containing numerous toxins and one of its constituent toxins in its findings of fact, where it characterizes the Coulter article as teaching that a composition “comprising Fab fragments reactive against a snake **toxin** is capable of neutralizing the lethality of that snake **toxin** *in vivo*.” [Third Decision at p. 8 (FF16).]

Just as the Third Decision repeatedly mischaracterizes the Coulter article as teaching neutralization of the lethality of whole snake **venom** when it only taught neutralization of the lethality of a single snake venom **toxin**, the Third Decision repeatedly mischaracterizes the claims. The claims require that the antivenom pharmaceutical composition “neutralizes the lethality of the **venom** of a snake of the *Crotalus* genus, but the Third Decision repeatedly characterizes the claimed invention as relating to neutralizing the lethality of a single snake venom **toxin**. [Third Decision at p. 23 (“effective in neutralizing the toxicity of toxins” “capable of neutralizing the toxicity of a toxin”).] And the Third Decision confuses a whole venom with a single one of its constituent toxins when characterizing Applicant’s examples. Applicants’ tested the ability of the antivenom pharmaceutical composition the neutralize the lethality of a whole snake venom by injecting the whole venom, not a single one of its constituent toxins. [Pages 18-22.] The Third Decision, however, mischaracterizes the examples as determining “lethality of the toxin by injecting a complex of toxin and immunoglobulin, or fragment thereof, into an animal.” [Third Decision at p. 10.]

Despite what the Third Decision says about the Coulter article, Applicant’s claims, and Applicant’s disclosure, the claims clearly require “neutralizing the lethality of the venom of a snake of the *Crotalus* genus,” and the Coulter article does not teach this element. Because the Coulter

article concerns neutralizing the lethality of a single constituent toxin, not whole venom, the PTO has not established that “the prior art included each element claimed.” MPEP § 2143 A. at p. 2100-129, col. 1; 72 Fed. Reg. at 57529, cols. 1-2. Because such a finding “must” be established for this rationale to apply, “this rationale cannot be used to support” the obviousness rejections.” MPEP § 2143 A. at p. 2100-129, col. 1; 72 Fed. Reg. at 57529, col. 2.

This rationale also cannot support the obviousness rejections because the PTO has not established that “one of ordinary skill in the art would have recognized that the results of the combination were predictable,” as is required. MPEP § 2143 A. at p. 2100-129, col. 1; 72 Fed. Reg. at 57529, col. 2. The Third Decision relied upon the teachings of the Coulter article to provide the reasonable expectation because the Coulter article teaches that its Fab fragments “retain their ability to neutralize the toxicity of a snake venom toxin.” [Third Decision on Appeal at pp. 18, 19 (“Coulter teaches that Fab fragments retain their intact parent immunoglobulin’s ability to neutralize the lethality of snake venom toxin.”), 20 (“Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake venom.”), 20-21 (“Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom.”), 21 (“Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake venom.”), (“Coulter supplied the key element required to satisfy the long-felt need”), p. 23 (“Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom”)]. As shown above, that basis relies upon a mischaracterization of the Coulter et al article.

Moreover, one of ordinary skill in the art would not have had a reasonable expectation that Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus would neutralize the lethality of the venom of a snake of the *Crotalus* genus based upon the Coulter article’s showing that Fabs neutralized the lethality of a single constituent toxin of *Psuedonaja textilis* venom. There would have been no reasonable expectation of success in neutralizing the lethality of *Psuedonaja textilis* venom as a whole by administering Fabs raised to just textilotoxin; there would have been no reasonable expectation of success in neutralizing the lethality of *Psuedonaja textilis* venom as a whole by administering Fabs raised to the entire venom; and there most certainly would have been

no reasonable expectation of success in neutralizing the lethality of *Crotalus* venom as a whole by administering Fabs raised to *Crotalus* venom—the claimed invention. [Dart Declaration at ¶ 21.]

First, there would have been no reasonable expectation of success in neutralizing the lethality of *Psuedonaja textilis* venom as a whole by administering Fabs raised to just textolotoxin . Snake venoms are very complex mixtures of small and large molecules, including numerous toxins. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 15, 47.] They are so complex that most have not had all their components fully characterized, despite decades of research. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 15.] Similarly, the properties of most venom components were not known in 1984, despite decades of research. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 16.] However, many of the most toxic components of snake venoms have been identified and their properties generally classified. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 16.] Thus, these toxins are sometimes referred to as, for example, neurotoxins, cardiotoxins, hemorrhagics, and fibrinolitics. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 16.] These properties are not necessarily exclusive, and a particular toxin may have more than one of these properties. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 16.] Moreover, the individual toxins can interact synergistically with other toxins in a venom. [Dart Declaration at ¶ 22; Russell Declaration at ¶ 16, 47.]

Nonetheless, most medically important venoms have been characterized in terms of the main toxic effect of their most clinically significant individual toxins, which can sometimes comprise a small percentage of a venom's total individual toxins. [Dart Declaration at ¶ 23; Russell Declaration at ¶ 16.] An antivenom must neutralize all of these clinically important toxins of a venom to neutralize the lethality of that venom. [Dart Declaration at ¶ 23; Dart and Horowitz, Chapter 5 in Envenomings and their Treatments (Bon and Goyffon ed. 1995) at pp. 83 ("An antivenom must be capable of neutralizing the injurious components of the venom."), 85 ("Thus, there may be a limited number of clinically important components that require neutralization."); Russell Declaration at ¶ 16.] Neutralizing the lethality of one toxin is not effective since other clinically important toxins could still cause lethality. [Dart Declaration at ¶ 23; Sanchez et al., 41

Toxicon 315-320 (2003) at p. 319 col. 2 ("venoms are complex mixtures of proteins and other toxic factors could cause death.") ("Both the hemorrhagic and fibrinolytic activities need to be neutralized with antivenom.").]

Psuedonaja textilis was known in 1984 to have several clinically important toxins. Neutralization of the lethality of only one of those toxins, as shown in the Coulter article, would not have been expected to result in neutralizing the lethality of the entire venom because the other lethal toxins would remain unneutralized. [Dart Declaration at ¶ 24.] Indeed, the existing *Psuedonaja textilis* antivenom suffers from this very problem. [Dart Declaration at ¶ 24.] It neutralizes the activity of textilotoxin, but it does not sufficiently neutralize the prothrombin activator, leading to coagulopathy and potentially fatal cerebral hemorrhage. [Dart Declaration at ¶ 24; Madras and Mirtschin, 24 Toxicon Reviews 79-94 (2005) at p. 80, first full paragraph. ("While CSL Ltd. antivenoms have saved many lives, persistent difficulties are being experienced with its inability to efficiently reverse the effects of the prothrombin activator. Unrelenting coagulopathy due to the slow reversal of prothrombin activator presents the added risk of cerebral hemorrhage to the victim.")] One of ordinary skill in the art would not have expected Coulter et al.'s Fab fragments to textilotoxin to have neutralized the lethality of the entire venom of *Psuedonaja textilis*. [Dart Declaration at ¶ 24.] Neutralizing one weapon in the venom's arsenal of lethal toxins would not neutralize the activity of its other lethal toxins. [Dart Declaration at ¶ 24.] Indeed, basic toxicology texts caution against extrapolating results from individual venom toxins to whole venoms. [Russell Declaration at ¶ 47.]

Second, there would have been no reasonable expectation of success in neutralizing the lethality of *Psuedonaja textilis* venom as a whole by administering Fabs raised to the entire venom. [Dart Declaration at ¶ 25.] Given the diversity in size, charge, and structure of snake venom toxins, Coulter et al.'s ability to obtain Fab fragments that neutralized the lethality of textilotoxin would not have provided a reasonable expectation that one of ordinary skill in the art could have obtained Fab fragments that neutralized the lethality of the other clinically significant *Psuedonaja textilis* venom toxins. [Dart Declaration at ¶ 25.]

An Fab fragment neutralizes the lethality of a venom toxin by binding to the toxin in such a way that it blocks the binding of the toxin to its target. [Dart Declaration at ¶ 26.] The Fab can itself block the binding of the toxin via stearic hindrance (physically or by polarity), or the Fab can alter the structure of the toxin. [Dart Declaration at ¶ 26; Russell Declaration at ¶ 44; Sullivan Declaration at ¶ 8.] In either case, the neutralization requires a specific binding between the Fab and the toxin. [Dart Declaration at ¶ 26.] The Fab must have a specific 3-D structure and charge to bind the toxin so that it blocks its binding to the target. [Dart Declaration at ¶ 26.] Otherwise, the Fab can bind to the toxin but have no effect on its activity. [Dart Declaration at ¶ 26; Dart and Horowitz at p. 86 ("it is crucial to understand that binding of a venom component does not necessarily mean neutralization."); Russell Declaration at ¶ 44; Sullivan Declaration at ¶ 8.]

The only commonality between textilotoxin and other clinically significant Psuedonaja textilis venom toxins is that they are contained in Psuedonaja textilis venom. [Dart Declaration at ¶ 27.] Like all snake venoms, Psuedonaja textilis venom is a complex mixture of very different molecules. [Dart Declaration at ¶ 27; Russell Declaration at ¶ 47.] Coulter et al.'s teaching that Fab could neutralize the lethality of textilotoxin would have provided no more guidance on the ability of Fabs to neutralize all the other clinically significant Psuedonaja textilis venom toxins than it provided on the ability of Fabs to neutralize any other combination of toxins. [Dart Declaration at ¶ 27.] Indeed, Dr. Dart is not aware of Coulter et al. ever producing a Psuedonaja textilis antivenom comprising Fab fragments despite the importance of Psuedonaja textilis antivenom to their employer, CSL Laboratories, which produced several Psuedonaja antivenoms. [Dart Declaration at ¶ 27.]

Third, there most certainly would have been no reasonable expectation of success in neutralizing the lethality of *Crotalus* venom as a whole by administering Fabs raised to *Crotalus* venom—the claimed invention. [Dart Declaration at ¶ 28; Russell Declaration at ¶ 47.] Even if Coulter et al. did produce an antivenom that neutralized the lethality of Psuedonaja textilis venom, one of ordinary skill in the art would not have had a reasonable expectation of success in extrapolating results with an antivenom to Psuedonaja textilis venom to an antivenom to *Crotalus* venom. [Dart Declaration at ¶ 28 Russell Declaration at ¶ 47.] The snakes are in two different

genera—Psuedonaja and Crotalus. [Dart Declaration at ¶ 28 Russell Declaration at ¶ 46.] Indeed they are in two different families—Elapidae and Crotalidae. [Dart Declaration at ¶ 28 Russell Declaration at ¶ 46.] There are significant differences between the venoms of those two families. [Dart Declaration at ¶ 28.] The venom of elapids, while a complex mixture of chemicals, is relatively simple for snake venom. [Dart Declaration at ¶ 28.] The venom of Crotalids, however, is extremely complex. [Dart Declaration at ¶ 28.] Indeed, while Psuedonaja venoms can have 3-4 lethal toxins, Crotalus venoms have at least 6 lethal toxins. [Dart Declaration at ¶ 28.] One of ordinary skill in the art would not have extrapolated antivenom results involving a single toxin of a relatively simple Psuedonaja venom to predict with any reasonable expectation of success what would happen with an antivenom to a much more complex Crotalus venom. [Dart Declaration at ¶ 28; Russell Declaration at ¶ 47.]

Because one of ordinary skill in the art would not have had a reasonable expectation that Fab fragments which bind specifically to a venom of a snake of the Crotalus genus would neutralize the lethality of the venom of a snake of the Crotalus genus based upon the Coulter article's showing that Fabs neutralized the lethality of a single constituent toxin of *Psuedonaja textilis* venom, the PTO has not established that "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." MPEP § 2143 A. at p. 2100-129, col. 1; 72 Fed. Reg. at 57529, cols. 1-2. Because such a finding "must" be established for this rationale to apply, "this rationale cannot be used to support" the obviousness rejections." MPEP § 2143 A. at p. 2100-129, col. 1; 72 Fed. Reg. at 57529, col. 2.

The MPEP and Guidelines require that, to establish a *prima facie* case under the second rationale:

Office personnel **must** articulate the following:

(1) a finding that the prior art contained a "base" device (method, or product) upon which the claimed invention can be seen as an "improvement;"

(2) a finding that the prior art contained a "comparable" device (method, or product that is not the same as the base device) that **has been improved in the same way as the claimed invention**;

(3) a finding that one of ordinary skill in the art could have applied the known "improvement" technique in the same way to the "base" device (method, or product) and the results would have been **predictable** to one of ordinary skill in the art; and

(4) whatever additional findings

MPEP § 2143 C. Use of Known Technique To Improve Similar Devices (Methods, or Products) in the Same Way, at p. 2100-132, col. 1 (emphasis added); 72 Fed. Reg. at 57530, col. 3. Not only must each of these findings be articulated, but this rationale cannot be used if a single one of these findings cannot be made. MPEP § 2143 C. at p. 2100-132, col. 1 ("If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art."); 72 Fed. Reg. at 57530, col. 3 (same).

This rationale cannot support the obviousness rejections because the Coulter article was not improved in the same way as the claimed invention and the results of improving Sullivan's antivenom by making and using Fab fragments in the same way as the Coulter article would not have been predictable. The Third Decision relies upon the Coulter article as teaching the Fab fragments neutralize the lethality of a snake venom and asserts that Applicants merely used a known technique to improve similar devices in the same way. [Third Decision at pp. 13, 16 (both quoting *KSR*.)]

As discussed in detail above, the Coulter article teaches neutralizing the lethality of a single constituent toxin of a snake venom, not the whole snake venom. Because the Coulter article does not teach neutralizing the lethality of a snake venom, the PTO has not established that Fab's venom neutralizing "has been improved in the same way as the claimed invention." MPEP § 2143 C. at p. 2100-132, col. 1; 72 Fed. Reg. at 57530, col. 3. Because such a finding "must" be established for this rationale to apply, "this rationale cannot be used to support" the obviousness rejections." MPEP § 2143 B. at p. 2100-131, col. 1; 72 Fed. Reg. at 57530, col. 3.

This rationale also cannot support the obviousness rejections because the PTO has not established that "the results [of applying the technique of the Coulter article to the antivenom of the Sullivan article] would have been predictable," as is required. MPEP § 2143 B. at p. 2100-130, col.; 72 Fed. Reg. at 57530, col. 1. As also discussed in detail above, one of ordinary skill in the art

would not have had a reasonable expectation that Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus would neutralize the lethality of the venom of a snake of the *Crotalus* genus based upon the Coulter article's showing that Fabs neutralized the lethality of a single constituent toxin of *Psuedonaja textilis* venom. Accordingly, the PTO has not established that "the results would have been predictable." MPEP § 2143 B. p. 2100-130, col. 2; 72 Fed. Reg. at 57530, col. 1. Because such a finding "must" be established for this rationale to apply, "this rationale cannot be used to support" the obviousness rejections." MPEP § 2143 B. at p. 2100-130, col.; 72 Fed. Reg. at 57530, col. 1.

The MPEP and Guidelines require that, to establish a *prima facie* case under the third rationale:

Office personnel **must** articulate the following:

- (1) a finding that there was **some teaching, suggestion, or motivation**, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, **to modify the reference or to combine reference teachings**;
- (2) a finding that there was **reasonable expectation of success**; and
- (3) whatever additional findings

MPEP § 2143 G. Some Teaching, Suggestion, or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention, at p. 2100-138, col. 2 (emphasis added); 72 Fed. Reg. at 57534 cols. 1-2. Not only must each of these findings be articulated, but this rationale cannot be used if a single one of these findings cannot be made. MPEP § 2143 G. at p. 2100-138, col. 2 ("If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art."); 72 Fed. Reg. at 57534, col. 1-2 (same).

This rationale cannot support the obviousness rejections because there was no teaching to modify the antivenom of the Sullivan article by using Fab fragments or to combine the antivenom teachings of the Sullivan article with the Fab fragment teachings of the Coulter article. The Third Decision relies upon the Coulter article as teaching that Fab fragments neutralize the lethality of a snake venom and asserts that this teaching would have led one of ordinary skill in the art to combine

the antivenom teachings of the Sullivan article with the Fab fragment teachings of the Coulter article. [Third Decision at pp. 13, 16 (both quoting *KSR*].

As discussed in detail above, the Coulter article teaches neutralizing the lethality of a single constituent toxin of a snake venom, not the whole snake venom. Because the Coulter article does not teach neutralizing the lethality of a snake venom, the PTO has not established a “teaching, suggestion, or motivation . . . to modify the reference or to combine reference teachings.” MPEP § 2143 G. at p. 2100-138, col. 2; 72 Fed. Reg. at 57534, col. 1-2. Because such a finding “must” be established for this rationale to apply, “this rationale cannot be used to support” the obviousness rejections. MPEP § 2143 G. at p. 2100-138; 72 Fed. Reg. at 57534, col. 1-2.

This rationale also cannot support the obviousness rejections because the PTO has not established that “there was a reasonable expectation of success,” as is required. MPEP § 2143 G. at p. 2100-138; 72 Fed. Reg. at 57534, col. 1-2.. As also discussed in detail above, one of ordinary skill in the art would not have had a reasonable expectation that Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus would neutralize the lethality of the venom of a snake of the *Crotalus* genus based upon the Coulter article’s showing that Fabs neutralized the lethality of a single constituent toxin of *Psuedonaja textilis* venom. Accordingly, the PTO has not established that “the results would have been predictable.” MPEP § 2143 G. at p. 2100-138; 72 Fed. Reg. at 57534, col. 1-2. Because such a finding “must” be established for this rationale to apply, “this rationale cannot be used to support” the obviousness rejections. MPEP § 2143 G. at p. 2100-138; 72 Fed. Reg. at 57534, col. 1-2.

Each of the rationales the PTO has offered for rejecting the claims requires that the PTO establish facts that it has not. Accordingly, the PTO has failed to establish a *prima facie* case of nonobviousness. “It is well settled that the PTO ‘bears the initial burden of presenting a *prima facie* case of unpatentability’” *Sullivan*, 498 F.3d at 1351 (quoting *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002)); MPEP § 2142 at p. 2100-137 col. 2 (“The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness”). “If the PTO fails to meet this burden, then the applicant is entitled to the patent.” *Glaug*, 238 F.3d at 1338; *In re Oetiker*, 977 F.2d 1443, 1445 (Fed., Cir. 1992)(“If examination at the initial stage does not produce a *prima facie*

case of unpatentability, then without more the applicant is entitled to grant of the patent.”); MPEP § 2142 at p. 2100-137 col. 2 (“If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.”). Accordingly, the obviousness rejections should be withdrawn, and the claims should be allowed.

IV. Extensive Evidence Would Rebut a *Prima Facie* Case If One Had Been Established

Evidence of unexpected results or objective evidence of nonobviousness (commercial success, long felt but unmet need, failure of others, praise of others, etc.) rebut a *prima facie* case of nonobviousness. MPEP § 2145 at p. 2100-162, col. 2, § 716.01(a).

A. The claimed invention yielded unexpected, superior results

Fab fragments had long been known to have potential application as an antidote, dating back at least to the use of Fabs to treat digoxin overdose in 1971. [Dart Declaration at ¶ 30; Smith et al, 36 Clin. Exp. Immunol. 384-396 (1979) at p. 385, first paragraph.] And many antivenoms that eliminated the Fc fragment had been made and used. [Dart Declaration at ¶ 30; Russell Declaration at ¶ 25; Sullivan Declaration at ¶ 5.] Those antivenoms, however, comprised Fab₂ fragments, not Fab fragments. [Dart Declaration at ¶ 30; Russell Declaration at ¶ 25; Sullivan Declaration at ¶ 5.] Fab₂ fragments differ from Fab fragments by being split from the Fc portion below the hinge rather than above the hinge. [Dart Declaration at ¶ 30; Russell Declaration at ¶¶ 23-24.] The result is that Fab₂ fragments comprise two antigen binding sites, still joined at the hinge, while Fab fragments split into two separate binding sites. [Dart Declaration at ¶ 30; Russell Declaration at ¶¶ 23-24.] Despite the relatively widespread use of antivenoms comprising Fab₂ fragments, particularly in Australia, nobody prepared an antivenom comprising Fab fragments before the Applicants. [Dart Declaration at ¶ 30; Russell Declaration at ¶ 25; Sullivan Declaration at ¶ 5.]

The evidence shows that nobody progressed to the smaller Fab fragments for two reasons. First, the Fab₂ fragment antivenoms were not as safe as had been anticipated, still resulting in

allergic reaction in 30-84% of cases. [Dart Declaration at ¶ 31; Dart and Horowitz at p. 90, second full paragraph; Russell Declaration at ¶¶ 25-26.] Second, the bivalence of Fab₂ fragments allows them to bind and cross-link two toxins, often resulting in a large Fab₂-toxin complex being precipitated out of solution; monovalent Fab fragments cannot do that. [Dart Declaration at ¶ 31; Russell Declaration at ¶¶ 27-29; Sullivan Declaration at ¶¶ 6,8.] The less than expected increase in safety of Fab₂ fragment antivenoms, combined with this potential for lower effectiveness of Fab₂ fragment antivenoms, prevented those skilled in the art from proceeding to Fab fragment antivenoms. [Dart Declaration at ¶ 31; Russell Declaration at ¶ 26.]

Despite those concerns, the Applicants prepared a Fab fragment antivenom and tested its ability to neutralize the lethality of *Crotalus* venom. [Dart Declaration at ¶ 32.] Unexpectedly, they found that the Fab fragment antivenom not only neutralized the lethality of *Crotalus* venom, but it did so both better than ACP and better than antivenom purified according to the Sullivan et al. article. [Dart Declaration at ¶ 32.] Table 1 shows that the Fab fragment antivenom protected 6 of 9 mice from death, while ACP protected only 3 of 9. [Dart Declaration at ¶ 32; Application at p. 19.] Table 2 shows that the Fab fragment antivenom protected 2 of 4 mice from death, while ACP protected only 1 of 4. [Dart Declaration at ¶ 32; Application at p. 20.] Table 3 shows that the Fab fragment antivenom protected 4 of 4 mice from death, as did the antivenom prepared according to the Sullivan et al. article, while ACP protected only 1 of 4. [Dart Declaration at ¶ 32 at p. 20.] Table 4 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Dart Declaration at ¶ 32; Application at pp. 20-21.] Table 5 shows that the Fab fragment antivenom protected 5 of 5 mice from death while the antivenom prepared according to the Sullivan et al. article protected 3 of 5, and ACP protected 0 of 5. [Dart Declaration at ¶ 32; Application at p. 21.] Finally, Table 6 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Dart Declaration at ¶ 32; Application at p. 21.] at p. 22.]

Even if one of ordinary skill in the art were to read the Coulter article as the Decision did—ignoring the very real and clinically important distinction between neutralizing the lethality of a toxin of a venom and neutralizing the lethality of the entire venom—these results are unexpected based on the Coulter article. [Dart Declaration at ¶ 33; Application at p. 21.] The Coulter article reported that Fab had the equivalent lethality neutralization ability as its corresponding IgG on a weight basis. [Dart Declaration at ¶ 33; Coulter article at p. 202, third paragraph.] IgG has a mass of approximately 150 kDa, while Fab has a mass of approximately 50 kDa. [Dart Declaration at ¶ 33; Application at p. 23.] Thus, 3 times as many Fab fragments need to be given to have the same lethality neutralizing ability as IgG according to the Coulter article. [Dart Declaration at ¶ 33.] Indeed, the Coulter article concludes that “Fab fragments can be obtained from rabbit IgG with losses of 20-30% of initial IgG antibody activity.” [Dart Declaration at ¶ 33; Coulter article at p. 202, last paragraph (emphasis added).] Applicants’ results surprisingly do not show such a loss in lethality neutralizing ability for an Fab fragment antivenom. [Dart Declaration at ¶ 33.] Instead, they show an increase in lethality neutralizing ability for an Fab fragment antivenom. [Dart Declaration at ¶ 33.]

This showing of an increase in lethality neutralizing ability, as opposed to the loss of up to 1/3 of the neutralizing ability expected in light of the Coulter article was certainly unexpected. Moreover, subsequent results provide still further evidence of this unexpected increase in lethality neutralizing ability.

This unexpected increase in effectiveness, combined with the increased safety, greatly interested clinicians in the field. [Dart Declaration at ¶ 33.] As the following claim chart shows, the assignee’s CroFab product is an embodiment of the claimed invention:

40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising	To obtain the final antivenin product [CroFab Product Insert at Drug Description.] CroFab is indicated for the management of patients with minimal or moderate North American crotalid envenomation. [CroFab Product Insert at Indications.]
Fab fragments which bind specifically to a venom of a snake of the <i>Crotalus</i> genus	CroFab® [Crotalidae Polyvalent Immune Fab (Ovine)] is a sterile, nonpyrogenic, purified,

	lyophilized preparation of ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep flocks immunized with one of the following North American snake venoms: <i>Crotalus atrox</i> (Western Diamondback rattlesnake), <i>Crotalus adamanteus</i> (Eastern Diamondback rattlesnake), <i>Crotalus scutulatus</i> (Mojave rattlesnake), and <i>Agkistrodon piscivorus</i> (Cottonmouth or Water Moccasin). To obtain the final antivenin product, the four different monospecific antivenins are mixed. Each monospecific antivenin is prepared by fractionating the immunoglobulin from the ovine serum, digesting it with papain, and isolating the venom-specific Fab fragments on ion exchange and affinity chromatography columns. [CroFab Product Insert at Drug Description.]
and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies,	<p>CroFab is a venom-specific Fab fragment of immunoglobulin G (IgG) [CroFab Product Insert at Mechanism of Action.]</p> <p>Papain is used to cleave the whole antibody into Fab and Fc fragments, and trace amounts of papain or inactivated papain residues may be present in CroFab. [CroFab Product Insert at Warnings.]</p> <p>Each monospecific antivenin is prepared by fractionating the immunoglobulin from the ovine serum, digesting it with papain, and isolating the venom-specific Fab fragments on ion exchange and affinity chromatography columns. [CroFab Product Insert at Drug Description.]</p> <p>The ovine immune serum from each flock is then digested with papain to produce antibody fragments (Fab and Fc), and the more immunogenic Fc portion of the antibody is then eliminated during purification. [Dart and McNally, 37 Annals of Emergency Medicine 181-188 (2001).]</p>
and a pharmaceutically acceptable carrier,	Each vial of CroFab contains up to 1 g of total protein and sodium phosphate buffer consisting

	<p>of dibasic sodium phosphate USP and sodium chloride USP.</p> <p>***</p> <p>The product is intended for intravenous administration after reconstitution with 10 mL of Sterile Water for Injection USP. [CroFab Product Insert at Drug Description.]</p>
wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the <i>Crotalus</i> genus.	<p>CroFab® [Crotalidae Polyvalent Immune Fab (Ovine)] is a sterile, nonpyrogenic, purified, lyophilized preparation of ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep flocks immunized with one of the following North American snake venoms: <i>Crotalus atrox</i> (Western Diamondback rattlesnake), <i>Crotalus adamanteus</i> (Eastern Diamondback rattlesnake), <i>Crotalus scutulatus</i> (Mojave rattlesnake), and <i>Agristron piscivorus</i> (Cottonmouth or Water Moccasin).</p> <p>***</p> <p>CroFab is standardized by its ability to neutralize the lethal action of each of the four venom immunogens following intravenous injection in mice. [CroFab Product Insert at Drug Description.]</p> <p>CroFab is indicated for the management of patients with minimal or moderate North American crotalid envenomation . . . [CroFab Product Insert at Indications.]</p> <p>CroFab was effective in neutralizing the venoms of 10 clinically important North American crotalid snakes in a murine lethality model (see Table 2). [CroFab Product Insert at Mechanism of Action.]</p>

CroFab was first scientifically reported in the Consroe et al. article in 1995. [Dart Declaration at § 34; Consroe et al, 53 Am. J. Trop. Med. Hyg. 507-510 (1995).] That article reported no adverse reactions in mice treated with CroFab. [Dart Declaration at § 34; Consroe et al,

at p. 509, col. 1.] In line with the surprising results reported in the Application, it also reported that CroFab was on average **5.2 times** more potent in neutralizing the lethality of *Crotalus* venom than ACP. [Dart Declaration at § 34; Consroe et al, at p. 509, col. 1.] This large increase in the ability to neutralize the lethality of a venom of a snake of the *Crotalus* genus is even greater than the increase shown in the application. And this 5-fold **increase** is strikingly greater than the 3-fold **decrease** predicted by the Coulter article. This unexpectedly improved result would rebut any *prima facie* case of obviousness. MPEP § 716.02(a) (“**GREATER THAN EXPECTED RESULTS ARE EVIDENCE OF NONOBVIOUSNESS**”); § 2144.09 (“**PRIMA FACIE CASE REBUTTABLE BY EVIDENCE OF SUPERIOR OR UNEXPECTED RESULTS**”).

B. Objective evidence would rebut any *prima facie* case

Objective evidence of nonobviousness, such as commercial success, long felt but unmet need, and praise of others, can rebut a *prima facie* case of nonobviousness. MPEP § 2145 at p. 2100-162, col. 2, § 716.01(a). Indeed, such evidence is “often most probative and determinative of the ultimate conclusion of obviousness or nonobviousness.” *Pro-Mold and Tool Co., Inc. v. Great Lakes Plastics, Inc.* 75 F.3d 1568 (Fed. Cir. 1996); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)(Objective evidence “may often be the most probative and cogent evidence in the record.”).

1. CroFab has enjoyed great commercial success

As shown above, CroFab is the assignee’s commercial embodiment of the claimed invention. CroFab’s greatly improved ability to neutralize the lethality of the venom of a snake of the *Crotalus* genus—an unexpectedly superior property—combined with its increased safety to capture almost the entire *Crotalus* antivenom market soon after its launch.

The results from the first CroFab clinical trial were reported, demonstrating that CroFab was in fact safe and effective in a clinical setting. [Dart Declaration at § 35; Dart and McNally.] CroFab was not approved until October 2000. [Dart Declaration at § 35.] According to Dr. Dart:

[a]fter the 1997 article, I received many emails from clinicians asking when CroFab would be available, and I continued to receive that question whenever I attended professional meetings. Clinicians were clamoring to get CroFab. The consensus among the inquiring clinicians, which I shared, was that **CroFab was so vastly superior to ACP in safety and in efficacy that it would completely supplant ACP in the market.**

[Dart Declaration at § 35. (emphasis added)]

The consensus among clinicians, including Dr. Dart, was correct. CroFab could not be produced fast enough to meet the initial demand, and Wyeth announced that it was going to discontinue production of ACP within a year of CroFab's launch. [Dart Declaration at § 36; Pink Sheet dated May 14, 2001 at p. 32.] According to Dr. Dart, "I recall Wyeth being vague about why they were discontinuing ACP, but those in the field viewed it as a recognition of what we all felt at the time; **CroFab was so vastly superior to ACP that we all wanted to use CroFab if given a choice.**" [Dart Declaration at § 36. (emphasis added)]

The attached data from IMS Health demonstrate this striking commercial success. Before the launch of CroFab, ACP had the entire market for treatment of *Crotalus* snake envenomation. In 1998, 24,000 vials of ACP were sold, and in 1999, 29,000 vials of ACP were sold. [IMS Health Data for 1998 and 1999.]

CroFab was launched in November 2000. It had very few sales that year due in part to being on the market for less than two months, and the fact that it is a seasonal product. The vast majority of *Crotalus* envenomations occur in warm weather; very few occur during winter. Thus, ACP retained almost all of the market in 2000 with 21,000 vials to less than 1,000 vials of CroFab sold. [IMS Health Data for 2000.]

In the very first year that CroFab was available for the entire year, it captured almost the entire market from ACP. In 2001, the entire market consisted of 24,000 vials. Of those 24,000 vials sold, 20,000 were CroFab, and only 4,000 were ACP. [IMS Health Data for 1998 and 1999.] ACP did experience production problems in 2001 [Pink Sheet dated May 14, 2001], but the immediate reversal of market share continued into the future.

In 2002, the entire market consisted of 21,000 vials. Of those 21,000 vials sold, 17,000 were CroFab, and only 4,000 were ACP. [IMS Health Data for 2002.] In 2003, the entire market consisted of 30,000 vials. Of those 30,000 vials sold, 26,000 were CroFab, and only 4,000 were ACP. [IMS Health Data for 2003.] In 2004, the entire market consisted of 40,000 vials. Of those 40,000 vials sold, 38,000 were CroFab, and only 2,000 were ACP. [IMS Health Data for 2004.] In 2005, the entire market consisted of 41,400 vials. Of those 41,400 vials sold, 38,900 were CroFab, and only 2,500 were ACP. [IMS Health Data for 2005.] In 2006, the entire market consisted of 43,800 vials. Of those 43,800 vials sold, 42,300 were CroFab, and only 1,500 were ACP. [IMS Health Data for 2006.] In 2007, the entire market consisted of 45,300 vials. Of those 45,300 vials sold, 44,600 were CroFab, and only 700 were ACP. [IMS Health Data for 2007.] In 2008, the entire market consisted of 43,400 vials. Of those 43,400 vials sold, 43,000 were CroFab, and only 500 were ACP. [IMS Health Data for 2008.] In 2009, the entire market consisted of 44,900 vials. Of those 44,900 vials sold, 44,700 were CroFab, and only 200 were ACP. [IMS Health Data for 2009.]

After taking over the majority of the market in its first full year on the market, CroFab now accounted for essentially all sales of antivenom for *Crotalus* snake envenomation. Some of that was undoubtedly due to Wyeth announcing in 2001 that it would discontinue ACP (although ACP continued to be sold for several years). However, clinicians believed that decision was in recognition of the fact that “CroFab was so vastly superior to ACP in safety and in efficacy that it would completely supplant ACP in the market” [Dart Declaration at § 35] and that “CroFab was so vastly superior to ACP that we all wanted to use CroFab if given a choice.” [Dart Declaration at § 36.]

The essentially immediate substitution of CroFab for ACP is particularly striking in light of the significant cost premium for CroFab. [Dart Declaration at § 37.] CroFab was more expensive per vial than ACP, and treatment requires more vials than ACP due to its shorter half-life. [Dart Declaration at § 37.] Standard dosing for a moderate envenomation with ACP would cost a hospital \$3,812.50-\$6,862.60, while treatment with CroFab would cost the hospital \$10,750-\$19,350—almost 3 times as much. [Dart Declaration at § 37; Seger et al., 24 Toxicol. Rev. 217-227 (2005) at

pp. 225-226.] Despite that significant cost premium, clinicians pushed their hospitals to stock CroFab and stopped ordering ACP soon after the launch of CroFab. [Dart Declaration at § 37.]

The essentially immediate substitution of CroFab for ACP is also particularly striking in light of the narrower indication Protherics sought and received for CroFab. In light of its resources as a small biotechnology company, Protherics did not perform studies necessary to obtain FDA approval for all envenomations but only “for the treatment of **minimal and moderate** North American Crotalidae envenomation.” [CroFab Product Insert at Indication (emphasis added).] In contrast, ACP was approved for “the treatment of envenomation caused by those crotalids (pit vipers) specified in the immediately preceding paragraph.” [ACP Product Insert at Indication.] Unlike CroFab, ACP’s approval was not limited to mild to moderate envenomations, but CroFab captured the entire market almost immediately.

The essentially immediate substitution of CroFab for ACP is particularly striking in light of the resources CroFab’s developer had at the time. CroFab was the first product approved for Protherics, which at that time was a small biotechnology company in Brentwood, Tennessee and London, Great Britain. With few resources, Protherics contracted out the marketing, filling, packaging, and distribution of CroFab, and experienced several supply shortages due to problems in that chain. Despite this lack of resources and these setbacks, CroFab took over the market essentially immediately.

Beyond the essentially immediate substitution of CroFab for ACP, CroFab’s ability to increase the market is also particularly striking. The market for antivenom to treat *Crotalus* envenomation was \$4.4 million in 1998, \$8.4 million in 1999, and \$8.2 million in 2000. [IMS Health Data for 1999-2000.] Protherics had estimated the market opportunity to be \$40 million in March 2001, after it had only had 5 months of CroFab sales. [Protherics 2001 Annual Report at pp. 5, 6.] The very next year, after only 1 full year of sales, Protherics **doubled** its estimate of the potential market for CroFab to \$80 million. [Protherics 2002 Annual Report at pp. 1.] That doubling of the predicted market was remarkably accurate as CroFab has sales of \$72.4 million in 2009. [IMS Health Data for 2009.] CroFab’s ability to increase the total market almost 10-fold

since the year of its launch is further striking evidence of commercial success due to the claimed invention.

2. CroFab has been praised by many

CroFab was featured in 6 of 10 episodes of the Animal Planet television series *Venom ER*, which was produced by the BBC. Applicants are filing these 6 episodes as 6 DVDs. In one scene a 9-year old girls is bitten by a rattlesnake, and the following statements occur at the indicated times during this scene:

3:50 Venom is highly complex. Each bite can cause very different reactions.

4:49 Shawn [Bush, the featured doctor] is using a brand new antivenom type: CroFab, the first new antivenom in 50 years.

5:29 From near death, Jenny makes a full recovery. **This new antivenom can make miracles happen.**

6:52 [regarding a CroFab shortage], without antivenom, people will die.

[Corinth Group Communications DVD. (emphasis added)] In another scene, Dr. Sean Bush is consulting by phone with a doctor using ACP because CroFab is not available:

26:50 Narrator: Wyeth [ACP] is the older antivenom, but CroFab stocks are getting so low that hospitals are having to use it as a last resort.

[Corinth Group Communications DVD.] In another scene, a woman is bitten by Sidewinder:

28:50 Because Wendy's been started on the old [ACP] antivenom, they decide to continue with it. But it's not as effective. Twice as much is needed to fight the venom. It takes longer to work. And it can cause complications.

30:01 Shawn's never treated a Sidewinder bite with CroFab, so perhaps using the older Wyeth antivenom is the better option. But there is a complication – a sudden recurrence of Wendy's asthma.

Dr. Bush: "it could be a side effect of the [ACP] antivenom.

[Corinth Group Communications DVD.]

Finally, a man has a reaction to CroFab while being treated:

37:02 Dr. Bush: We're just starting this medicine. It's an antivenom for snake bites. There's risk involved with a snake bite. There is also risk involved with the

antivenom. So far there hasn't been any severe adverse reaction to this antivenom but there could be.

37:18 Past treatments came with a big risk of reaction, but these are much reduced in CroFab. And it will stop the venom progression.

42:25 Donald [the patient] is sick, reacting to the antivenom that's supposed to be saving him. The team must adapt their treatment. Reactions like this were common to the old antivenom. But this reaction to CroFab is another first for Shawn.

43:00 But every bite is different, everybody is different. There is something in Donald that's reacting to the antivenom.

45:31 Dr. Bush: This is the most severe adverse reaction to CroFab that I've seen so far. Now when I used the old antivenom [ACP], we would see this kind of reaction routinely and in fact we saw much more severe reactions. And fortunately this reaction resolved fairly quickly.

Another aspect of CroFab that has been praised is the ability to treat a patient with the antivenom a second time for a second snake bite. Given the high occurrence and severity of immune reactions to ACP, this was not previously possible. Patients could die from the immune reaction to the ACP. One snakebite patient who had told doctors he had previously been treated with antivenom and reacted to it was given antivenom due to the severity of his envenomation symptoms. "Minutes later, Brown was dead." ["Man allergic to antitoxin dies," *The Sunday Tennessean* (September 13, 1987).] In contrast, a doctor successfully treated a snake bite victim with CroFab **six different times** and observed no immune reactions. This was such a contrast to past experience with ACP that they wrote a Letter to the Editor of a medical journal. [Wilson, 20 Am. J. Emerg. Med. Online.]

After Hurricane Katrina, the FDA requested that Protherics increase supplies of CroFab to meet the expected increase in rattlesnake bites due to floodwaters driving the snakes from their habitats. ["Snake Antivenin Drug Maker Stands Out During Hurricanes," *Tyler Courier-Times-Telegraph* (January 15, 2006).] And aides to President Bush ordered a permanent supply of CroFab for his ranch in Texas in 2003 because it "had gained such a worldwide reputation." ["Serum Success," *Weekly News* (April 19, 2003).] Finally, one patient who was treated with CroFab for a rattlesnake envenomation likes to call CroFab, "Crofabulous." [www.blogher.com/bitten-rattlesnake-part-2-antivenin-gets-lost (accessed June 7, 2010).]

3. CroFab satisfied a long-felt but unmet

In 1984, the only commercially available antivenom for envenomation by North American snakes of the Crotalidae family was Antivenin (Crotalidae) Polyvalent (equine origin) (ACP). [Russell Declaration at ¶ 19, 21.] However, immune reactions to ACP had long been known to be a problem. [Dart Declaration at ¶ 29; Russell Declaration at ¶ 21.] Over 75% of patients treated with ACP developed some reaction. [Russell Declaration at ¶ 21.] The problem was so great that some clinicians refused to give ACP, and others felt stuck between the rock of not treating a snake bite victim with an antivenom and the hard place of treating a snake bite victim with an antivenom that might be worse for the victim than the venom being treated. [Dart Declaration at ¶ 29.]

The immune reactions were mainly attributed to 1) extraneous protein in the antivenom and 2) the presence of the Fc portion of the IgG molecules. [Dart Declaration at ¶ 29.] The immune reaction had long contributed to extensive research on modifying existing antivenoms to reduce the immune reactions. [Russell Declaration at ¶¶ 22, 43.] The Sullivan et al. article addressed the first cause of those reactions by affinity purifying the IgG molecules that actually bound four target Crotalus venoms. [Dart Declaration at ¶ 29.] Before Applicants' invention, however, nobody had successfully addressed the second aspect of this long-felt need for a safer antivenom, despite the major concern clinicians had regarding allergic reactions to ACP. [Dart Declaration at ¶ 29.] CroFab, the assignee's commercial embodiment of the claimed invention, met this long felt by unmet need.

As discussed above, the PTO has not established a prima facie case of nonobviousness. Even if the PTO had established a prima facie case, this extensive evidence of nonobviousness would rebut such a prima facie case. MPEP § 2145 at p. 2100-162, col. 2, § 716.01(a). Accordingly, the obviousness rejections should be withdrawn, and Applicants request the timely issuance of a Notice of Allowance.

V. Request for an Interview

Applicants respectfully request that, if the Examiner has any remaining rejections or other questions or concerns in light of the extensive evidence of nonobviousness submitted with this amendment, the Examiner contact the undersigned at the phone number listed below. Interviews can “serve to develop and clarify specific issues and lead to a mutual understanding between the examiner and the applicant, and thereby advance the prosecution of the application.” MPEP § 713.01; Director’s Forum: David Kappos’ Public Blog, May 28, 2010 entry (listing an interview as the #1 tip for advancing prosecution), January 26, 2010 entry (“I encourage our patent examiners to . . . continue conducting interviews at any point in the examination process where an interview makes sense”). Applicants believe that any actions that would expedite prosecution of this pre-GATT application would be in the interest of the public, as well as themselves.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. P0786.70000US05 from which the undersigned is authorized to draw.

Dated: June 29, 2010

Respectfully submitted,

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